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FULBRIGHT & JAWORSKI L.L.P. 600 CONGRESS AVE. SUITE 2400 AUSTIN, TX 78701			SINGH, ANOOP KUMAR	
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			1632	

DATE MAILED: 10/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/518,599

Applicant(s)

PENNINGER ET AL.

Examiner

Anoop Singh

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 August 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 67-69,73 and 98-103 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 67-69,73 and 98-103 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 8/8/06.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Applicant's response and amendment to claims filed August 8, 2006 has been received and entered. Applicants have added claims 98-103. Claims 67-69, 73 and 98-103 are pending in this application.

Election/Restrictions

Applicant's election with traverse of the invention of group II (claim 67-69) filed on February 3, 2006 was acknowledged. Applicant argument of examining group II with group IV was found persuasive and therefore these groups were rejoined for examination purposes. The restriction requirement between group I and II is withdrawn in view of applicants clarification and deletion of term agonist from the pending claim 67.

Accordingly, a method of treating an ACE2 decreased state comprising administering to a mammal therapeutically effective amount of ACE2 activator and by co-administering ACE2 activator with ACE inhibitor will be examined in the instant application.

Claims 1-66, 70-72 and 74-97 were cancelled by the amendment filed on February 3, 2006.

Newly submitted claims 98-103 are directed to an activator that is subsequently limited to a polynucleotide or a polypeptide. It is emphasized newly amended claims limit the activator to include polynucleotide or polypeptide; therefore, these claims will be examined to an extent they are directed to elected invention.

Claims 67-69, 73, 98-103 are under consideration.

Drawings

The drawing/figures are objected to because tables and sequence listings included in the specification must not be duplicated in the drawing. See C.F.R. 1.58(a) and § 1.83. Applicants are advised that upon issuance of a patent, the complete text of the sequence listing submitted in compliance with 37 C.F.R § 1.821-1.825 will be published as part of the patent. Applicants should amend the specification to delete any figures which consist only of nucleic acid or protein sequence which have been submitted in their entirety in computer readable format (as SEQ ID Nos) (See Figure 10a, 10b and 11).

Specification

The disclosure is objected to because of the following informalities: The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See page 14, lines 17-18.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 67-69, 73, 98-103 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the

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evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Claim 67 is drawn to a method of treating an ACE2 decreased state comprising administering to a mammal having an ACE2 decreased state a therapeutically effective amount of an ACE2 activator. Claim 68 limits the mammal of claim 67 to include human, while claim 69 limits the decreased Ace2 state to include hypertension, congestive heart failure, chronic heart failure, acute heart failure, myocardial infarction, arteriosclerosis, renal failure, and/or lung disease. Claim 73 limits the method to include co administration of ACE2 activator and ACE inhibitor. Subsequent claims 98-99 and 103 limit the activator to include Ace2 polypeptide and nucleic acid encoding polypeptide. It is also noted that claims 100-102 limit the decreased Ace2 state to include lung disease, subsequently limiting to adult respiratory distress syndrome and lung cancer.

The aspects considered broad are: the breadth of subject population, any method of administration to affect genus of conditions resulting from ACE decreased state, treating genus of disease associated with ACE2 decreased state by genus of ACE2 activator subsequently limiting to administering a ACE2 polypeptide or a nucleic acid encoding and ACE2 polypeptide.

It is noted that as recited, claimed invention reads on a broad genera of gene and protein therapy. Specific considerations for *in vivo* protein and gene therapeutic transfer such as fate of the protein or DNA vector itself (e.g. volume of distribution, rate

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of clearance into tissue) and consequences of altered gene expression and protein production, have to be addressed for an *in vivo* protein or gene therapy method of treating ACE2 decreased state in a mammal. Additionally, considerations for gene transfer include selection of a vector system for sufficient term expression of the therapeutic protein and regulation of its expression in target cells. Although Applicant's specification teaches role of ACE2 is a critical negative regulator of heart contractility and heart function in a ACE2 knockout mouse model, however, the specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to (i) how an artisan of skill would have practiced the claimed method in any mammal, (ii) the claimed method would have resulted in providing the ACE2 in deficient cells in amount sufficient to treat genus of diseases associated with ACE2 decreased state by administering ACE2 polypeptide/activator or nucleic acid encoding ACE2 protein to any site. An artisan would have to carry out extensive experimentation to practice the invention, and such experimentation would have been undue because art of gene/ protein therapy and gene delivery *in vivo* is unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced in any mammal. As will be shown below, these broad aspects as well as limitations were not enabled for the claimed invention at the time of filing of this application because neither the specification nor the art of record taught sufficient guidance to practice the claimed invention. For purposes to be shown in the state of the prior art, the question of lack of enablement is discussed.

The invention describes compositions and methods for use in diagnosing and treating heart, lung and kidney diseases, including hypertension, coronary heart disease, heart and kidney failure, lung edema, and lung injury such as in toxic shock or artificial ventilation (pp 1). The specification contemplates new paradigm for the regulation of the renin -angiotensin system and shows a completely new and unexpected usage of ACE2 (page 2). Pages 2-7 broadly summarize the invention and provide a brief description of figures. Pages 7-31 provide a detailed description of preferred embodiments, therapeutic methods, screening of ACE2 activator, knockout mammals kits, definition of terms, and other therapeutic aspects of ACE2 and characterization of ACE2 as a negative regulator of RAS and its role in blood pressure control. Pages 31-44 describe specific example showing studies in ACE2 knockout mice and mapping of ACE2 to QTL on the X-chromosome in hypertensive rat strains.

While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to be desired organs continued to be unpredictable and inefficient. For example, numerous factors complicate the gene delivery art that cannot be overcome by routine experimentation. These include, the fate of DNA vector itself, volume of distribution, rate of clearance in tissue, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of RNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ significantly based on the vector used and the

protein being produced (Goodman & Gilman's The Pharmacological basis of Therapeutics, McGraw-Hill, New York, NY. pp 77-101).

Given this lack of reasonable predictability in Applicant's specification and the art, the Artisan would require a large amount of information from Applicant's examples to provide the guidance to provide reasonable predictability. Examples in the instant application describes ACE2 mapping to a QTL on the X-Chromosome in three hypertensive rat strains, it is noted that ACE2 in mouse and rat is predominantly expressed in kidney and heart, with little expression in lung and liver (see Figure 1c and example). The specification also exemplified that ACE2 protein expression was markedly reduced in SBH/y animals that are fed a normal diet, while an increase in blood pressure of SBH/y rats following a 4-week diet of DOCA-salt correlated with further decreased ACE2 protein expression (see Figure 2B). It is emphasized that specification describes that in order to test whether ACE2 has any essential role in the cardiovascular physiology and the pathogenesis cardiovascular diseases, the mouse ACE2 gene was cloned and an ACE2 knockout mouse was made (see example and Figure 3a-c). It is noted that loss of ACE2 had no apparent direct effect on blood pressure homeostasis in this defined mouse background however backcross with mutant mice to other mouse backgrounds show the role of ACE2 in blood pressure control similar to human (see example and Figure 4). The western blot of kidney of these ace2 deficient mice show enhanced expression of hypoxia inducible factor-1alpha (HIF1-.alpha.) and vascular endothelial growth factor (VEGF). The examples further describe specific phenotype of this knockout mice showing slight wall thinning of the left

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ventricle and increased chamber dimensions (see Figure 5) and anterior left ventricular wall (AW) and increase in the left ventricle end diastolic dimension. It further characterizes that ACE2 functions as a negative regulator of the RAS and controlling endogenous levels of AngII. Using double knock out specification shows that ablation of ACE expression on an *ace2* mutant background completely abolished the heart failure phenotype of *ace2* single knockout mice (see figure 8a-c). Specification describes that ACE2 knockout mice showed a significantly more severe response in lung elastance than wild type mice. Thus, specification contemplates the significance of ACE2 in protecting lungs from acute acid-induced injury (see example, pages 40-43). However, such broad disclosure does not demonstrate the information required by the Artisan to reasonably predict that any protein or transgene can be expressed in any cell of any mammal at therapeutic effective levels. The art of protein and gene therapy and their delivery at the time of the filing of this application was unpredictable wherein any gene was expressed in an individual suffering from cardiovascular or lung disorder.

The specification does not disclose the effectiveness of the method of the instant invention in treating any ACE2 decreases state. Nor does it teach the effectiveness of the method in increasing the level of ACE2 in any cell and reversal of any pathology or condition associated with decreased ACE2 state. The specification only teaches role of ACE2, but fails to disclose any method in treating any condition by administering any composition of ACE2. In summary, specification as filed does not teach how nucleic acid encoding ACE2 administered via any route to any mammal could transduce any cells such that any active ACE2 is translated. Furthermore, It is noted that the

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specification does not provide any guidance as to how much vector should to be delivered for transduction of cells in organ of any animal that would be adequate for therapeutic response. The method of gene therapy and gene delivery in a animal specifically in humans was not routine, rather was unpredictable at the time of filing of this application as neither art of record nor the specification teaches how to practice the claimed inventions.

The claims as recited do not require the nucleic acid molecule is part of an expression vector or otherwise operably linked to any regulatory sequences, such as a promoter. The specification only provides guidance on the manufacture and use of retroviruses, adenoviruses, adeno associated virus (AAV), herpes virus vectors, such as vaccinia virus vectors, HIV and lenti virus-based vectors, or plasmids (Specification page 11). It does not provide guidance on the use of naked nucleic acid molecules, lacking a promoter in the claimed method. Further, the literature at the time of filing does not provide guidance on how to get RNA polymerase to efficiently prime to a DNA strand that lacks a promoter. Therefore, the skilled practitioner would be unable to practice the claimed invention in a manner commensurate in scope with the claims, except with a vector comprising a regulatory sequence operably linked to a nucleic acid molecule. The specification teaches only the role of ACE2 in the heart failure, hypertension and lung pathology, but fails to disclose the efficacy of using said any method wherein administering a ACE2 composition resulted in the treatment of any disorder. The examples in the specification do not disclose a therapeutic effect in any patient after therapy with any composition and/or treating with any composition.

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Although working examples are not required, particularly in predictable art, the presence or absence of working example is one of the factors that must be considered, particularly in the unpredictable arts. In the absence of specific guidance, one of ordinary skill in the art would be required to engage in undue experimentation to make and use the invention as claimed.

At the time of filing, gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses or plasmid DNA/liposome complexes, was considered highly unpredictable. Verma et al states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene " (Verma et al, 1997, Nature, 389, pp 239, col. 3, para 2). The state of the prior art effectively summarized by the references of Verma and Somia (1997) Nature 389:239-242 and Pfeifer and Verma (2001) Annual Review of Genomics and Human Genetics.2: 177-211 describes progress made in developing new vectors and also suggest vector targeting *in vivo* to be unpredictable and inefficient. Verma et al review various vectors known in the art for use in gene therapy and problems associated with each implying that at the time of claimed invention resolution to vector targeting had not been achieved in the art (Verma et al., 1997; Pfeifer et al., 2001; entire article). They highlight some advantages of using retroviral and adeno-associated viral vector in gene therapy but also acknowledge a greater level of skepticism in using these vectors in human (Pfeifer et al., 2001; abstract). It is noted by the authors that more efficient and safe vectors are required to deliver gene to the target cell for therapeutic effective level

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of gene expression (Pfeifer and Verma 2001, Annual Review of Genomics and Human Genetics.2: 177-211, pp 201). It is also noted that claim 102 limit the ACE2 decreased state to include lung cancer, however, prior to instant invention art teaches that treating any subject having cancer by gene therapy was unpredictable. For instance, Vile et al (Gene Therapy, 2000, 7: 2-8) describe the unpredictability of gene delivery in the treatment of cancer and state, "Gene therapy for the treatment of cancer was initiated with high levels of optimism and enthusiasm. Recently, this perception has had to be tempered by the realization that efficiency and accuracy of gene delivery remain the most significant barriers to its success. So far, there has been a disappointing inability to reach target cells with sufficient efficacy to generate high enough levels of direct killing and this has necessitated the invocation of bystander effects in order for any potential strategy to be convincing" (abstract). The specification does not provide any specific guidance to overcome this art recognized unpredictability in introducing vector encoding ACE2 or ACE2 polypeptide or any other activator for the desired therapeutic response in any subject.

The scope of invention as claimed encompasses a method for treating ACE2 decreased state in a mammal by introducing a nucleic acid encoding a polypeptide or a polypeptide via any route of administration (i.e oral, intranasal, intramuscular, intravenous, subcutaneous etc.). It has been difficult to predict the efficacy and outcome of transduced therapeutic gene or polypeptide because several factors govern the expression and/or therapeutic potential of transduced gene *in vivo*. The transduction of target cells represent the first critical step in any gene based therapy, which not only

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depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors. In addition, besides the limitations in gene transfer the problem to selectively target cells *in vivo* is still one of the most difficult obstacles to overcome (as discussed before, *supra*). For example, upon systemic administration the viral and non-viral particle may bind to many cells they encounter *in vivo* and therefore would be diluted before reaching their targets. The specification merely contemplates plurality of route without providing any specifics or showing that other routes of administration would result in expression of transgene in heart, kidney or lung for the treatment of plurality of disorder. The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to how an artisan of skill would have practiced the claimed method in human by administering claimed compositions via any route. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because art of the gene delivery was not routine rather it was unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

Next, it is noted that because the mechanism of development of each disease is different, the parameters of treating any particular disease associated with ACE2 decreased state such as heart failure may be different, from those used in treating another disease such as lung cancer and therefore, the reversal of the symptoms in one case due to any therapy can not be predictive of the effects in another. Such parameters will include the site of action of the transgene or protein, cell types and

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tissues affected by the ACE2 deficiency. In the instant case, specification has exemplified most of its finding in a ACE2 knockout mice. It is emphasized that the mere capability to perform gene transfer in mouse is "not" enabling because a desired phenotype cannot be predictably achieved by simply introducing transgene construct of the types described in the specification. The specification teaches the different phenotype of ACE2 knockout mice and ACE/ACE2 double knockout mice. Holschneider et al. (Int J Devl Neuroscience, 2000, 18: 615-618) state that single genes are often essential in a number of different physiological processes. Hence deletion of an individual gene in the instant case CPR may prove so drastic or so widespread as to create an amalgam of phenotypes whose interpretation becomes confounded by the interaction of various new physiologic changes (pp 615). Holschneider et al discuss various factors that contribute to the resulting phenotype of transgenic mice, including compensatory system that may be activated to mask the resulting phenotype; these compensatory changes may be due to differential expression of another gene, which may be regulated by the downstream product of the deleted gene. Thus, the specification at best provide some evidence of role of ACE2 deficiency in hypertension and lung disorders using a transgenic knock out mice, but these findings could not be predictive of any method of treating any condition by delivering a nucleic acid or ACE2 protein. It is noted that claims as recited and the specification is silent about whether a nucleic acid encoding ACE2 protein or ACE2 polypeptide would be in active form when administered via any route at any site as broadly recited in rejected claims. Therefore, these molecules may not even act as an activator. It is also noted decreased ACE2

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decreased state include plurality of cardiac disorder including atherosclerosis. Prior to instant invention, Tailleux et al (2003) describe that lipid and lipoprotein metabolism is dissimilar between mice and humans. In addition, the regulations of genes encoding proteins that are involved in lipid and lipoprotein metabolism are not identical between humans and mice and thus data obtained in the mouse are not always directly relevant to humans. Third, the mouse is highly resistant to atherosclerosis and does not develop atherosclerotic lesions spontaneously. Tailleux et al further teach, "homologous recombination technology allows the extinction of a specific gene (knockout). However, in such mouse models, the functionality of all metabolic pathways is not necessarily maintained, and thus the model only provides information about whether a ligand requires the presence of the deleted gene. However, in most murine models created by genetic modification, lipoprotein levels are insufficiently altered to induce the development of atherosclerotic lesions. Thus, in absence of any direct evidence in the specification or prior art it would be difficult to predict the role of administering ACE2 activator. Thus, at the time of filing, the resulting phenotype of a knockout was considered unpredictable. Furthermore, contrary to applicants finding prior art teaches a method of treating an ACE-2 associated state in humans suffering from a blood pressure related disorder, such as congestive heart failure by administering a therapeutically effective amount of an ACE-2 inhibiting compound, such that the ACE-2 associated state is treated (Acton et al US Patent no 6,632,830). Furthermore, Acton et al contemplate administering an effective amount of an ACE-2 inhibiting compound and an effective amount of an ACE inhibitor to treat cardiac conditions which is contrary to

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the teaching of instant application that intend to treat same conditions by administering ACE2 activator (see column 3, lines 54-67 bridging to column 4). Therefore, the observations of Acton et al in the prior art and the stand taken that phenotypes disclosed in the instant application cannot be solely due to loss of ACE2 gene. It is apparent that in absence of any specific showing that administering nucleic acid encoding ACE2 polypeptide or Ace2 protein would results in result in any therapeutic effect, an artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because of the art of treating cardiac or lungs condition by administering ACE2 activator showed conflicting results and was not completely resolved at the time of filing of this application.

The specification also contemplates delivering polypeptides to any cells using *in vivo* delivery vehicles such as but not exclusive to liposomes. In summary, specification does not specifically provide any specifics in term of what and where the therapeutic composition would be administered for an optimal therapeutic response, it is noted that, there are art-recognized limitations of using liposome and there is no teaching or contemplation as to how an artisan of skill would have addressed these limitations. For example, Fillion et al (Br J Pharmacol. 1997;122(3): 551-557) listed several adverse effects associated with cationic lipids or cationic liposome (table 2, pp 18) such as immunomodulation of animals, complement activation, induction of pulmonary inflammation and toxicity. The specification does not provide any guidance as to what doses of the cationic lipid would be used in the method without eliciting adverse effects. It is noted that the prior art at the time of filing of this application did not provide any

guidance in this regard either. Davis et al (Current Opinion in Biotechnology 2002, 13:128–131) evinces an optimistic outlook for non-viral delivery system but states “perfect system does not currently exist”. Davis et al describe problems associated with non-viral delivery system, which includes obstacles in manufacturing, toxicity, formulation and stability.

With regards to evaluation of efficacy of a therapeutic protein, dosing, clearance and efficacy of the product, preclinical evaluation for toxicity and immunogenicity are important steps. It is noted that toxicity with proteins often presents differently that with small-molecule pharmaceutical drugs (Scientific Considerations Related to Developing Follow-On Protein Products, 2004, p. 3, paragraph 1). Further, immunogenic responses in patients can be triggered by large-molecules products, product-related or process-related impurities raising unwanted antibodies. Additionally, the way in which unwanted immunogenicity may present in different patients is unpredictable and varied, even with identical amino acid sequences; immunogenicity to the product can vary dramatically (Scientific Considerations Related to Developing Follow-On Protein Products, 2004, p. 4-5). Thus, preclinical evaluation for efficacy and immunogenicity of a therapeutic protein is vital for the development of therapeutic protein. It is noted that, it is important to assess the half-life and clearance of the protein as the terminal elimination half-life of related products can vary drastically. For example, six companies manufacture FDA-approved versions of human growth hormone, with the same number of amino acid and very similar molecular weights, presented terminal half-life from 1.75 to 10 hours. Thus, such large variations can impact the effectiveness

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of the product and the as the body's immune response to it (Scientific Considerations Related to Developing Follow-On Protein Products, 2004, p. 5, paragraph 1). Hence, the risk of immunogenicity should be assessed for each product and characterized with appropriate therapeutic response. In the instant case, specification provides no guidance of administering any polypeptide for the treatment of any condition associate with ACE decreased state.

In relation to the use of any type of vector to express the nucleic acid encoding a ACE2 polypeptide. Applicants contemplate the use of a variety the vectors including adenovirus, adeno-associated virus. Prior art teaches the challenging issues faced in the applications of vectors for gene therapy and the need to use of a gene delivery system that is efficient, safe, non-immunogenic and allows for short or long-term protein expression as required by the target. A reasonable correlation must exist between the scope of the claims and scope of enablement set forth in the specification as filed. Without sufficient guidance, the mere enumeration of a number of vectors to highly express a nucleic acid encoding ACE2 protein for the treatment of genus of diseases associated with decreased ACE2 state in any mammal is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

With regards to evaluation of a therapeutic protein, dosing, clearance and efficacy of the product, Prior art teaches that preclinical evaluation for immunogenicity are important steps. The specification contemplates administration of an ACE2 in a manner that increases the level of ACE2 by direct administration; however, the

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specification fails to teach any immunogenicity or efficacy of any such composition in any mammal because of said administration. Hence, one skill in the Art at the time of the invention could not reasonably predict that the use of Ace2 for protein therapy will treat any condition associated with ACE2 decreased state in any mammal.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions. The specification and prior art do not teach a method of *in vivo* delivery of any ACE2 activator such that it transduces cells sufficiently to elicit a pharmacological response for a desired duration in any tissue of any mammal suffering from any condition associated with decreased ACE2 state. An artisan of skill would have required undue experimentation to practice the method as claimed because the art of gene and protein therapy and *in vivo* delivery and treatment of any condition associated with ACE2 decreased state in general by gene and protein delivery *in vivo* was unpredictable at the time of filing of this application as supported by the observations in the art record.

Withdrawn-Claim Rejections-Written description - 35 USC § 112

Applicant's arguments with respect to claims 67-69 and 73 have been considered but are moot in view of the new ground(s) of rejection.

New grounds of Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 67-69, 73 and 98-103 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claimed inventions encompass a method of treatment of an ACE2 decreased state by administering to a mammal therapeutically effective amount of any ACE2 activator. In the instant case, the claims are broadly directed to a method of treating plurality of conditions by administering mammals any ACE2 activator. This genus comprises plurality of activators that may further have subspecies. The claims and specification broadly discloses ACE2 activators that encompass ACE2 nucleic acid, its fragments, ACE 2 polypeptides, its fragment, and compounds that enhances ACE2 activity. The specification contemplates that activators would preferably be directed to specific domains of ACE2 and target unique sequences of ACE2 (pp 15 of the specification, lines 10-14) to increase ACE2 activity. The specification does not describe the complete structure of any other ACE2 activator except mouse, rat and human ACE2 sequences. A skilled artisan could not predict the structure of the any other ACE2 activator that includes genus of compound that must show contemplated biological

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activity nor could a skilled artisan predict the structure of any fragments of nucleic acid or protein sequence in all different species that must show contemplated biological activity. Although specification describes that activators are preferably directed towards specific domains of ACE2 to increase ACE2 activation (see paragraph 59). In addition, specification does not provide any disclosure as to what would have been the required structure for any compound and that would show contemplated biological activity.

Therefore, possession of an ACE2 nucleic acid, peptide in rat, mouse or human and identification of zinc binding site HEMGH domain, catalytic centers and trans membrane domain does not predict the characteristics of administering any other nucleic acid or polypeptide fragments to mammal showing contemplated biological activity. It is also noted that neither specification nor art of record provide any evidence that any such fragment of polynucleotide encoding ACE2 or ACE2 polypeptide would be active to elicit any biological activity. The specification at best only provides evidence some role of ACE2 in hypertension and cardiac disorder that may be due to indirect consequence of lack of ACE2 in knock out mice that could be attributed to alteration of other critical pathways (*supra*). *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111 (Fed Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1117. The specification does not "clearly allow person of ordinary skill in the art to recognize that he or she invented what is claimed." *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The factors to be considered when assessing possession of the claimed invention include disclosure of complete or partial structure, physical and/ or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is the requirement that the activator to be administered treat genus of cardiac and lung disease. The specification does not contemplate any specific functionally equivalent fragments, thereof encoded by an ACE2 nucleic acid. The specification only describes the full-length nucleic acid molecules. While the specification attempts to define the various domain thereof encoded by ACE2 by their possession of one or more of the bioactivities of the ACE2 protein, this definition is so broad as to encompass a vast number of structurally unrelated proteins. However, the specification does not specify what structural and functional characteristics must be retained by this potentially vast genus of proteins fragments in order to function in the claimed method.

Accordingly, in the absence of sufficient recitation of a distinguishing identifying characteristic of the genus of fragments and compounds, the specification does not provide adequate written description of the claimed genus of fragments of ACE2 nucleic acid or ACE2 protein fragments or compounds that enhance ACE activity that are defined solely by their ability to enhance ACE2. No identifying characteristics of a compound or other fragments of ACE2 are disclosed. Further without a clear teaching of the essential elements of the claimed ACE2 activator and lack of identifying characteristics, a skilled artisan cannot envision the detailed structure of all the variants, fragments and compounds that must show the contemplated biological activity.

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Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity/simplicity of the structure and/or methods disclosed in specification.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, Applicant was not in possession of the genus of all the different ACE2 activator that included fragments of ACE2 polypeptide and nucleic acid encoding ACE2 effective in mammals as encompassed by the claims. *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 67-69, 73 and 98-103 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting

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to a gap between the steps. See MPEP § 2172.01. It is noted that independent claims 67 and 103 recite administering and activator that is either nucleic acid encoding ACE2 or ACE2 polypeptide for treating genus of disease including lung cancer, but the claim does not set forth any steps involved in method/process, it is unclear what method/process applicant is intending to encompass. The claim merely recites a gene therapy/protein therapy method without any active, positive step delineating how claimed method would actually be practiced. Claims 68-69, 73 and 98-102 directly or indirectly depend on claim 67. Appropriate correction is required.

Maintained-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 67-68 remain rejected under 35 U.S.C. 102(b) as being anticipated by

Acton et al (US Patent no. 6194556, dated 02/27/2001, effective filing date 12/11/1997).

Claim 67 is directed to a method of treating an ACE2 decreased state comprising administering to a mammal having an ACE2 decreased state a therapeutically effective amount of ACE2 activator. Claim 68 limits the mammal of claim 67 to include human.

Acton et al teach a method for treating disease or disorder that is associated with aberrant ACE-2 level or activity or which can benefit from modulation of the activity or level of ACE-2 (col. 7, lines 41-43). Acton et al describe the term "modulation" to refer both up regulation (activation) and down regulation (col. 14, lines 28-32). Thus, teachings of Acton et al encompass a method of treating an ACE2 decreased state comprising administering a therapeutic effective amount of ACE2 agonist. Acton et al further teach the methods for treating hypertension, CHF, inflammatory reactions, and methods to reduce pain. The methods of Acton et al comprise administering pharmaceutically effective amount of a composition comprising an ACE-2 therapeutic either locally or systemically to a subject (col. 7, lines 45-52). Thus, teachings of Acton et al encompass all the limitation of the instant application.

Accordingly, Acton et al anticipate claims 67-68.

Response to Arguments

US Patent no. 6194556

Applicant's arguments filed August 8, 2006 have been fully considered but they are not persuasive. Applicants argue that '556 patent predicts that ACE2 antagonists

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would be useful in treating hypertension. Applicants argue that this is in contrast to the disclosure in the present specification, which provides different paradigm for the regulation of rennin-angiotensin system. Applicants assert that specification discloses that hypertension and other cardiac disease are the result of an ACE2 decreased state. Applicants also argue that only therapeutic uses of an activator contemplated by '556 patent are for the treatment of inflammation, burn and insect bites.

In response to applicant's arguments, the recitation of Ace2 decrease state has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., prediction of mechanism, treatment of hypertension and other cardiac disorder) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In the instant case, rejected claims merely recite in preamble a method of treating an ACE2 decreased state, which simply requires administering to a mammal having an ACE2 decreased state an ACE2 activator. In fact, applicants are arguing a limitation

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that is recited in claim 69, which further limits the ACE2, decreased state to include specific conditions is not rejected by '556. Applicants argument of use of Ace2 activator for treating hypertension as well as other condition is totally misplaced and has no basis for what has been claimed. Since, Action et al contemplated modulation of ACE2 activity by administering a therapeutic effective amount of ACE2 agonist to replenish ACE2 activity irrespective of its intended therapeutic effect that are not required by the rejected claims. Therefore, it is clear that Acton et al completely anticipate claims 67-68.

Withdrawn-Claim Rejections - 35 USC § 102

Claims 67-68 and 73 rejected under 35 U.S.C. 102(e) as being anticipated by Acton et al (US Patent application no. 6,632,830, dated 10/14/2003, filing date 04/28/2000) is withdrawn in view of the applicants argument that Acton et al teach combination of ACE inhibitor along with an ACE2 antagonist.

Withdrawn-Claim Rejections - 35 USC § 103

Claims 67-69 and 73 rejected under 35 U.S.C. 103(a) as being unpatentable over Acton et al (US Patent application no. 6,632,830, dated 10/14/2003, filing date 04/28/2000) and Crackower et al (American Journal of Hypertension, April, 2001, 14 (4)

Part 2, pp. 78A) is withdrawn in view of Applicant's arguments that combining the teaching of Crackower et al would change the principle of operation of '830 patent.

Conclusion

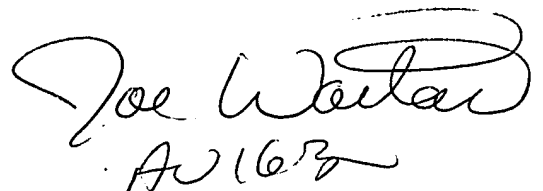
No Claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272- 0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh, Ph.D.
Examiner, AU 1632


AU 1632